Clinical Pharmacokinetics of Alfentanil, Fentanyl and Sufentanil
An Update

Jens Scholz, Markus Steinfath and Martin Schulz

1 Department of Anaesthesiology, University of Hamburg, University Hospital Eppendorf, Hamburg, Germany
2 Drug Information Center, Federal Union of German Associations of Pharmacists (ABDA), Eschborn, Germany

Contents

Summary .............................................................................................................. 275
1. Basal Pharmacokinetic Characterisation ..................................................... 276
2. Mode of Administration .............................................................................. 278
3. Factors Affecting the Pharmacokinetics ....................................................... 281
   3.1 Age ......................................................................................................... 281
   3.2 Obesity .................................................................................................. 283
   3.3 Plasma Protein Content ........................................................................ 283
   3.4 Acid-Base Status .................................................................................. 284
   3.5 Liver Disease ....................................................................................... 284
   3.6 Renal Insufficiency .............................................................................. 285
   3.7 Cardiopulmonary Bypass ..................................................................... 286
4. Pharmacokinetic Interactions .................................................................... 286
5. Rational Selection of Opioids ..................................................................... 287
6. Conclusions ................................................................................................. 289

Summary

Alfentanil, fentanyl and sufentanil are synthetic opioid analgesics acting at specific opioid receptors. These opioids are widely used as analgesics to supplement general anaesthesia for various surgical procedures or as primary anaesthetic agents in very high doses during cardiac surgery. Fentanyl and sufentanil especially are administered via infusion for long term analgesia and sedation in intensive care patients.

Opioid analgesics are mainly administered using the intravenous route. However, other techniques of administration, including epidural, intrathecal, transdermal and intranasal applications, have been demonstrated.

Important pharmacokinetic differences between alfentanil, fentanyl and sufentanil have been shown in many reports. Alfentanil has the most rapid analgesic onset and time to peak effect as well as the shortest distribution and elimination half-lives. The volume of distribution and total body clearance of this agent are smaller when compared with those of fentanyl and sufentanil.

The pharmacokinetics of the opioid analgesics can be affected by several factors including patient age, plasma protein content, acid-base status and cardio-
The endogenous opioid peptides and the opioid receptors, including their subtypes which have already been cloned, constitute a complex physiological pain relieving system. Opioid receptors are coupled to guanine nucleotide-binding regulatory proteins (G proteins) which mediate cellular effects such as inhibition of adenylate cyclase, activation of potassium channels, and inhibition of voltage-dependent calcium channels, resulting in various well known opioid-related effects.

Over the past 30 years, Paul Janssen and his associates have been extremely successful in developing a clinically relevant series of synthetic opioids specifically acting at the opioid receptors. Fentanyl, the first of the 4-anilinopiperidine series of opioid agonists, is a chemical congener of the reversed ester of pethidine (meperidine), and was introduced into clinical practice in the early 1960s. The more recently developed drugs, such as alfentanil (which has the shortest half-life after bolus administration) and sufentanil (the more potent), offer a greater selection for practical use.

Alfentanil is predominantly, if not exclusively, metabolised by cytochrome P450 (CYP) 3A4. Fentanyl undergoes phase I metabolism, predominantly by oxidative N-dealkylation, and sufentanil is metabolised by N-dealkylation at the piperidine and amide nitrogens as well as by O-demethylation.